Docket No.: JJJ-P02-540
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Sampath et al.

Application No.: 09/613177 Confirmation No.: 8978

Filed: July 10, 2000 Art Unit: 1637

For: METHODS AND COMPOSITIONS FOR IDENTIFYING MORPHOGEN ANALOGS Examiner: J. N. Fredman

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

A Notice of Appeal was filed on April 19, 2005. The deadline for filing an Appeal Brief is June 19, 2005. Applicants are concurrently petitioning for a two-month extension of time, extending the deadline for filing a response to August 19, 2005. Accordingly, this Appeal Brief is being timely filed within the extended period and is in furtherance of said Notice of Appeal. This brief is submitted in triplicate in accordance with the provisions of 37 C.F.R. § 1.192 (a).

The fees required under § 41.20(b)(2), and any required petition for extension of time for filing this brief and fees therefor, are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

I.	Real Party In Interest
II	Related Appeals and Interferences
III.	Status of Claims
IV.	Status of Amendments
V.	Summary of Claimed Subject Matter

I. REAL PARTY IN INTEREST

The real parties in interest for this appeal are:

Curis, Inc., the assignee of the application, and Johnson & Johnson Inc., the licensee of the application.

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

To the best of the knowledge of the undersigned, there are no other appeals, interferences or judicial proceedings known to the Appellant, the Appellant's legal representative, or the above-noted real party of interest that will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 25 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 11,12, 14, 16-29, 34-35, 37-42
2. Claims withdrawn from consideration but not canceled: None
3. Claims pending: 1-10, 13, 15, 30-33, 36 and 43-50
4. Claims allowed: 15, 30-32
5. Claims objected: 4, 5, 7, 8, 10 and 33
6. Claims rejected: 1-3, 6, 9, 13, 36, and 43-50

C. Claims On Appeal

The claims on appeal are claims 1-3, 6, 9, 13, 36, and 43-50.

IV. STATUS OF AMENDMENTS

In response to a Final Office Action dated 19 November 2004, Applicants filed an Amendment on 22 February 2005. The Examiner entered the amendment and mailed an Advisory Action on 16 March 2005. In the Advisory Action, the Examiner indicated that Applicants' arguments and proposed amendments to claims 4, 5, 7, 8, 10, 15, 30-33 did not place any claims in condition for allowance. Applicants filed a communication in response to the Advisory Action on 19 April 2005, which included a terminal disclaimer. The communication was entered. A second advisory action was mailed on 28 April 2005 allowing claims 15 and 30-32, objecting to claims 4, 5, 7, 8, 10 and 33, and rejecting claims 1-3, 6, 9, 13, 36, and 43-50.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Applicants provide the following concise summary of the invention as recited in the specification:

> The invention described herein capitalizes on the discovery that morphogens, particularly OP-1, can affect expression of certain genes, present naturally in the genome of mammalian cells. That is, stimulation of mammalian cells with a morphogen such as OP-1 induces a spectrum of biological effects, including but not limited to the transcriptional activation of selected cellular genes. The promoter region of at least one such gene has been analyzed and, as disclosed herein, found to comprise a morphogen responsive transcription activating element. Following contact of the cell with the exemplary OP-1, the transcription activating element specifically induces transcription at least of a gene(s) which is situated downstream of and operatively associated with the element. This specific transcriptional activation involves binding of one or more intracellular substances ("expression activators") to the OP-1 responsive transcription activating element. These intracellular substances bind with portions of the preferred responsive transcription activating element naturally disposed within the promoter region of the mammalian type X collagen gene, at a 5' region of the element which is A/T rich resembling an MEF-2 consensus sequence, and at an adjacent 3' region thereof resembling an AP-1 binding site sequence. It is shown herein that deletion or mutation of the morphogen responsive transcription activating element results in loss of OP-1 responsive transcriptional activation of the downstream gene(s) operatively associated with the element (page 13, lines 1-16).
>
> The present methods and compositions accordingly exploit the morphogen responsive properties of the newly-discovered transcription activating element. Generally, the methods and compositions of the present invention provide the skilled artisan with the analytical tools and technical know-how sufficient to identify substances (morphogen analogs) that can mimic a biological effect induced by a morphogen such as OP-1. Guidance provided herein accordingly

> will facilitate evaluation of a variety of diverse substances for morphogen analog properties, thereby broadening the spectrum of potential therapeutic candidates for amelioration and/or treatment of diseases, injuries and deteriorative disorders, such as metabolic bone diseases, for which morphogens are anticipated to provide clinical benefit (page 13, line 17 to page 14 line 4).

Although those teachings are summarized above, the Board is strongly urged to study the specification before considering the rejections on appeal.

VI. GROUNDS OF OBJECTION TO BE REVIEWED ON APPEAL

The issues to be decided in this appeal is as follows:

(1) Whether claims 1-3, 6, 9, 13, 36, 43-47, 49 and 50 are unpatentable under 35 USC § 103 over Harris (U.S. Pat. No. 6,083,690) in view of Smart (U.S. Pat. No. 5,650,276) and in further view of Nadal-Ginard (WO94/18239).

(2) Whether claims 1, 13, 36, 43 and 45-50 are unpatentable under 35 USC § 103 over Harris (U.S. Pat. No. 6,083,690) in view of Smart (U.S. Pat. No. 5,650,276) and further in view of Ozkaynak (U.S. Pat. No. 5,652,118).

VII. GROUPING OF THE CLAIMS

Claims 1 and 36 are independent claims. Claims 1 and 36 stand and fall together with respect to both issues (1) and issue (2).

Claims 2, 3, 6, 9, 13 and 43-50 depend, directly or indirectly, on claim 1 and stand and fall together with this claim. Claim 36 has no dependent claims. Claims 2, 3, 6, 9, 13 and 43-47, 49 and 50 stand and fall together with claim 1 with respect to issue (1); claims 13, 43 and 45-50 stand and fall together with respect to issue (2).

VIII. ARGUMENT

Issue 1: Rejections of Claims 1-3, 6, 9, 13, 36, 43-47, 49 and 50 Under 35 U.S.C. § 103(a)

The Examiner alleges that claims 1-3, 6, 9, 13, 36, 43-47, 49 and 50 are unpatentable under 35 U.S.C. § 103(a) over Harris in view of Smart and in further view of Nadal-Ginard.

A. Failure of the References to Teach All the Elements of the Claims

MPEP 706.02(j) requires, among other things, that the prior art references teach or suggest all the claim elements in order to establish a *prima facie* case of obviousness. Applicants

respectfully submit that the Examiner has not provided adequate rationale as to why Nadal-Ginard, in combination with Harris and Smart, teaches or suggests all the features of claim 1, *i.e.* the Examiner has failed to show that the combination of these three references teach or suggest the claimed invention.

Neither of these three references on their own, nor the combination of references, teach or suggest all the elements of claims 1 and 36. For example, claim 1 recites, in part, a "test cell comprising a DNA comprising: (i) a transcription activating element that is responsive to, and distinct from the gene encoding, said morphogen." The combination of the cited references, however, fails to teach or suggest a transcription activating element ("TAE") that is (1) distinct from the gene encoding said morphogen and (2) responsive to the morphogen for screening compounds.

Harris

Harris teaches the use of transcription activating elements found in the morphogen genes themselves *i.e.* TAEs that are present in the DNA sequences of morphogen genes such as those from the mouse BMP-4A gene. Harris however, does not describe TAEs found in downstream genes which are regulated by morphogens *i.e.* genes that are downstream in the signal transduction pathway. Column 4, lines 32-42 of Harris makes this point very clearly, reciting as follows:

> The present invention is distinguished from other techniques for identifying bone-active compounds, as it specifically identifies chemical compounds, agents, factors or other substances which stimulate bone cells to produce the bone growth factors in the bone morphogenetic protein (BMP) family (hereinafter "osteogenic agents"). These osteogenic agents are identified by their capacity to increase the activity of the promoters of genes of members of the BMP family and other bone growth factors which are normally produced by bone cells, and other cells including cartilage cells, tumor cells and prostatic cells. (Emphasis added).

Harris recites reads on column 2, lines 33-40, as follows:

> Also provided in accordance with the present invention are isolated DNA sequences encoding a promoter region of at least one bone morphogenetic protein, and a system for identifying osteogenic agents comprising an expression vector comprising such promoter sequences operatively linked to a reporter gene encoding an assayable product, and means for detecting the assayable product produced in response to exposure to an osteogenic compound. (Emphasis added).

A schematic representation of morphogen signaling and of the teachings of Harris is shown as **Appendix A**. The top panel shows a cell expressing an endogenous morphogen and a second

cell having a downstream target of the gene whose expression is regulated by the morphogen. The second panel shows a diagram of the screening method of Harris. As described above, the method of Harris relies on a cell expressing a DNA comprising a morphogen TAE and a reporter gene.

By contrast, claims 1 and 36 recite the TAE of the downstream genes which morphogen proteins regulate, not promoter regions or transcription response elements from morphogen genes, as diagrammed in the bottom panel. Thus, Harris fails to teach or suggest a screening method using a downstream TAE that is responsive to the morphogen as recited in the claims 1 and 36.

Harris in view of Smart

Not only does Harris fail to teach or suggest a downstream TAE or how it could be used in a screening method, Smart fails to correct this deficiency. Smart describes methods of screening candidate compounds for the ability to modulate the protein level of a morphogenic protein in a cell. This is diagrammed on the third panel of Appendix A. The teachings of Harris and Smart are both limited to identifying agents which regulate the gene expression of morphogen genes; Harris by monitoring transcription from promoters of morphogen genes and Smart by monitoring the level of morphogen protein in a cell. The combined teachings of Harris and Smart do not teach or suggest TAEs from non-morphogen genes, let alone their use in screening assays. In fact, Smart does not teach TAEs from any gene.

Harris in view of Smart in further view of Nadal-Ginard

Not only does Harris in view of Smart fail to teach or suggest every element of claim 1, Nadal-Ginard fails to correct this deficiency, *i.e.* the combined teachings of Harris, Smart and Nadal-Ginard fail to teach or suggest all the claim elements of claim 1. Harris in view of Smart and in further view of Nadal-Ginard fails to teach or suggest a method for identifying a compound that induces a morphogen-mediated biological effect using a downstream TAE responsive to the morphogen, as recited in the pending claims.

The Examiner has conceded that Harris and Smart do not teach every element of claim 1 as evidenced by the withdrawal of the obviousness rejection based on Harris/Smart in the Office Action mailed on 19 November 2004 (see page 3, section 5). The Examiner, however, failed to articulate in that Office Action or in a subsequent advisory action how Nadal-Ginard rectified this deficiency. As explained above, the combined teachings of Harris and Smart fail to teach a downstream TAE that is responsive to the morphogen, and Nadal-Ginard fails to teach or

suggest this claim feature, even when combined with Harris and Smart. In fact, Applicants were unable to find any reference in Nadal-Ginard that relates to a morphogen, *i.e.* Nadal Ginard does not have any references to morphogen proteins, morphogen receptors, morphogen genes, biological activity of morphogens, or TAEs that are responsive to morphogens.

The Office Action of 19 November 2005 alleges on page 9, third paragraph, the following:

> ...Nadal-Ginard expressly teaches "The agent can affect e.g. induce or enhance, the expression of a pocket protein. (See page 17, lines 20-21.) So Nadal-Ginard expressly teaches the new requirement of an agent, such as a morphogen, which induces the expression of a different protein. This is particularly exemplified in claim 4 of Nadal-Ginard, in which expression of a reporter construct that is dependent upon interaction of a candidate agent with the promoter sequence of a candidate agent with the promoter sequence of a downstream gene.

In response to this allegation, applicants submit that, as stated previously, Nadal-Ginard does not teach, or even mention, morphogens. Accordingly, the statement that Nadal-Ginard teaches morphogens which induce the expression of a different protein is unfounded. Furthermore, applicants submit that claim 4 of Nadal Ginard, at best, relates to the use of a reporter gene operably linked to a gene or gene segment that is responsive to one of the transcription factors, but not to a TAE that is responsive to a morphogen.

And even if Nadal Ginard taught DNA sequences of TAE's, Nadal-Ginard does not teach that any of those DNA sequences are responsive to morphogens. In other words, even if Nadal-Ginard had disclosed a sequence which was subsequently shown by others to be a TAE responsive to a morphogen, Nadal-Ginard or its combination with Harris/Smart, fails to teach that such elements would be useful in the screening methods. The combination of these three references, then, fails to render the claimed method obvious.

B. Lack of Motivation to Combine Smart/Harris/Nadal-Ginard

According to MPEP 706.02(j) and MPEP 2142, some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present to make a *prima facie* case of obviousness.

The Examiner has failed to show a motivation or suggestion to combine Harris with Smart, or Harris/Smart with Nadal-Ginard. Harris and Smart both relate to methods of screening

agents that regulate the expression of morphogen genes themselves (see Appendix A for schematic diagram). The method of Harris uses TAEs from morphogen genes linked to a reporter gene to identify agents which increase levels of morphogen mRNA in a cell. The method of Smart directly monitors the ability of agents to increase the level of morphogen protein in a cell, without the use of reporters. The Examiner has failed to provide a motivation to combine these two screening methods with each other, and therefore has failed to make a prima facie case of obviousness.

And even if, for arguments sake, the methods of Harris and Smart were combined, any resulting method would still be limited to identifying agents which modulate morphogen gene expression, since Harris and Smart relate to identifying agents capable of regulating the expression level of morphogens themselves. Accordingly, there may be, at best, motivation to further combine Harris/Smart with references that taught TAEs from morphogen genes, but there would be no motivation or suggestion to combine then with references that taught TAEs from genes responsive to morphogen. Not only is motivation to combine the references lacking, the Examiner has failed to set forth an alleged motivation or suggestion for combining Harris/Smart with Nadal-Ginard. Accordingly, the Examiner has failed to make a *prima facie* case of obviousness.

Issue 2: Rejections of Claims 1, 13, 36, 43 and 45-50 Under 35 U.S.C. § 103(a)

The Examiner alleges that claims 1, 13, 36, 43 and 45-50 are unpatentable under 35 USC § 103 over Harris in view of Smart and further in view of Ozkaynak (U.S. Pat. No. 5,652,118).

A. Failure of the References to Teach All the Elements of the Claims

MPEP 706.02(j) requires, among other things, that the prior art references teach or suggest all the claim elements in order to establish a *prima facie* case of obviousness. Applicants respectfully submit that the Examiner has not provided any rationale as to why Ozkaynak, in combination with Harris and Smart, teaches all the features of claim 1, *i.e.* has failed to show that the combination of these three references teaches the claimed invention.

As set forth in the arguments under Issue 1 above, Harris in view of Smart fails to teach every element of claims 1 and 36, from which all other rejected claims depend. In particular, Harris and Smart fail to teach a screening method that uses TAEs that are responsive to the

morphogen. At best, Harris in view of Smart teaches a method of screening agents using TAEs found in morphogen genes.

Ozkaynak fails to correct the deficiencies of Harris and Smart *i.e.* Harris in view of Smart in further view of Ozkaynak fail to teach or suggest all the elements of claims 1 and 36. The Examiner conceded in the Office Action mailed on 19 November 2004, by withdrawing the obviousness rejection based on Harris/Smart, that Harris and Smart in combination do not teach every element of claim 1. However, that Office Action failed to show how the combined teachings of Harris/Smart/Ozkaynak allegedly teach all the features of the rejected claims. The Examiner has failed to show even how Ozkaynak alone teaches or suggests a TAE that is responsive to a morphogen.

As summarized in the abstract, Ozkaynak teaches BMP-3 sequences and their uses: "[d]isclosed are (1) nucleic acid and amino acid sequences for a novel morphogenic protein; (2) methods for producing and expressing the protein in a biologically active form; and (3) methods for utilizing the protein to induce tissue morphogenesis in a mammal." Ozkaynak does not teach TAEs responsive to morphogens, or even TAEs in morphogen genes themselves.

The Office Action mailed on 19 November 2004 alleges that Ozkaynak teaches that morphogens induce CAM expression, particularly N-CAM expression, as part of their induction of morphogenesis, and further alleges that "Ozkaynak teaches a downstream expression, here N-CAM, which is a promoter distinct from the gene encoding a morphogen" (emphasis added) (page 9, lines 15-16).

In response, applicants first submit that Ozkaynak does not teach that all morphogens regulate N-CAM. The Example 3.5 on column 29 of Ozkaynak relates to the induction of N-CAM expression only by the morphogen OP-3. OP-3, however, is not a morphogen recited in claim 1. Instead, claim 1 recites OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vg1, Vgr-1, DPP, or 60A. Therefore, Ozkaynak does not teach that the morphogens recited in the claims are capable of inducing N-CAM expression, let alone teach a TAE responsive to OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vg1, Vgr-1, DPP, or 60A.

And even if Ozkaynak taught that all morphogens regulated N-CAM expression, which applicants do not concede, the Examiner has confused the terms "gene", "promoter" and "TAE". While Ozkaynak may teach that morphogens regulate N-CAM expression, Ozkaynak does not teach or suggest that there is a TAE responsive to morphogens within the N-CAM gene or within its promoter. In fact, Applicants were unable to find the term "promoter" in the

specification of Ozkaynak, except with respect to viral promoters used in expression constructs. While the Examiner alleges that N-CAM is a promoter distinct from a morphogen, this observation is irrelevant. The claims do not recite promoters. They recite TAEs, and Ozkaynak fails to teach TAEs.

The allegation by the Examiner that Ozkaynak teaches TAEs, let alone in N-CAM promoters, is baseless. Even if the N-CAM gene were to have a TAE responsive to morphogens, Ozkaynak does not teach or suggest the identity of the TAE. Ozkaynak fails to teach or suggest the location of the TAE within the N-CAM gene, or within the N-CAM promoter (if that were the location of the TAE), or even the DNA sequence of the alleged TAE. In summary, Ozkaynak fails to disclose the presence or identity of a TAE responsive to a morphogen.

In summary, Ozkaynak does not teach or suggest, *inter alia* (i) that the N-CAM gene has a TAE, (ii) where such an hypothetical element would be located (e.g. which section of the promoter, intron, intergenic regions, etc.), or (iii) describe the sequence of the TAE. This failure to teach a TAE responsive to morphogens is not remedied by combining the teachings of the references. As stated in the previous sections, Harris and Smart likewise fail to teach or suggest TAEs responsive to morphogens. The combined teachings of the three references, then, do not teach every feature of the claims, and therefore do not render the claims obvious.

B. Lack of Motivation to Combine Harris/Smart/ Ozkaynak

Even if Ozkaynak had implicitly or explicitly taught or suggested a TAE responsive to a morphogen, which applicants do not concede, no motivation or suggestion exists for combining the teachings of Harris/Smart with Ozkaynak, and the Examiner has failed to set forth a motivation or suggestion in the Office Action.

Harris and Smart relate to identifying agents capable of regulating the expression level of morphogens themselves. There may be, at best, a motivation to further combine Harris/Smart with references that teach TAEs from morphogen genes. But this is not what Ozkaynak teaches. Ozkaynak teaches OP-3 sequences and the uses of such sequences. Again, even if there was a motivation to combine the references, the combined teachings would not teach or suggest all the claim features of the invention. At best, combining the three references may result in a method of screening agents which increase OP-3 protein levels, or increase transcription from an OP-3 transcriptional unit; it would not result in a method for identifying agents that increase

transcription from downstream TAEs.

C. Lack of Motivation to Combine Harris and Smart with *Any* Reference Simply Teaching TAEs that Are Responsive to Morphogens

Even if the Examiner had cited a reference that actually taught a TAE responsive to one of the morphogens recited in the claims, no motivation exists to combine such reference with Harris and Smart. The methods of Smart and Harris are confined to monitoring transcription from morphogen promoters or monitoring morphogen protein levels. There is no suggestion or motivation to monitor anything else, and certainly no motivation to fundamentally alter the combined assays of Harris and Smart to monitor transcription of downstream genes. Therefore, even a reference disclosing downstream genes, or even TAEs responsive to morphogens from downstream genes, would not be properly combined with Harris and Smart.

IX. APPENDIX (DIAGRAMS AND CLAIMS)

A copy of the claims involved in the present appeal is attached hereto as Appendix B. As indicated above, the claims in Appendix B include the amendments filed by Applicant on February 22, 2005. Claims that are allowed or objected to are not included. The Advisory Action mailed on April 28, 2005 indicated that the claims that were objected to *i.e.* claims 4, 5, 7, 8, 10 and 33, would be allowable if rewritten to include all the elements of the base claim and any intervening claims. Accordingly, these objected claims are not included in the listing of claims and are not the subject of this appeal.

X. EVIDENCE

No evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the Examiner is being submitted.

XI. RELATED PROCEEDINGS

No related proceedings are referenced in II. above, or copies of decisions in related proceedings are not provided, hence no Appendix is included.

Applicant believes no fee is due other than the $500 fee for filing an Appeal Brief and the $450 for a two-month extension of time. However, if an additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. JJJ-P02-540 from which the undersigned is authorized to draw.

Dated: July 29, 2005

Respectfully submitted,

By _____

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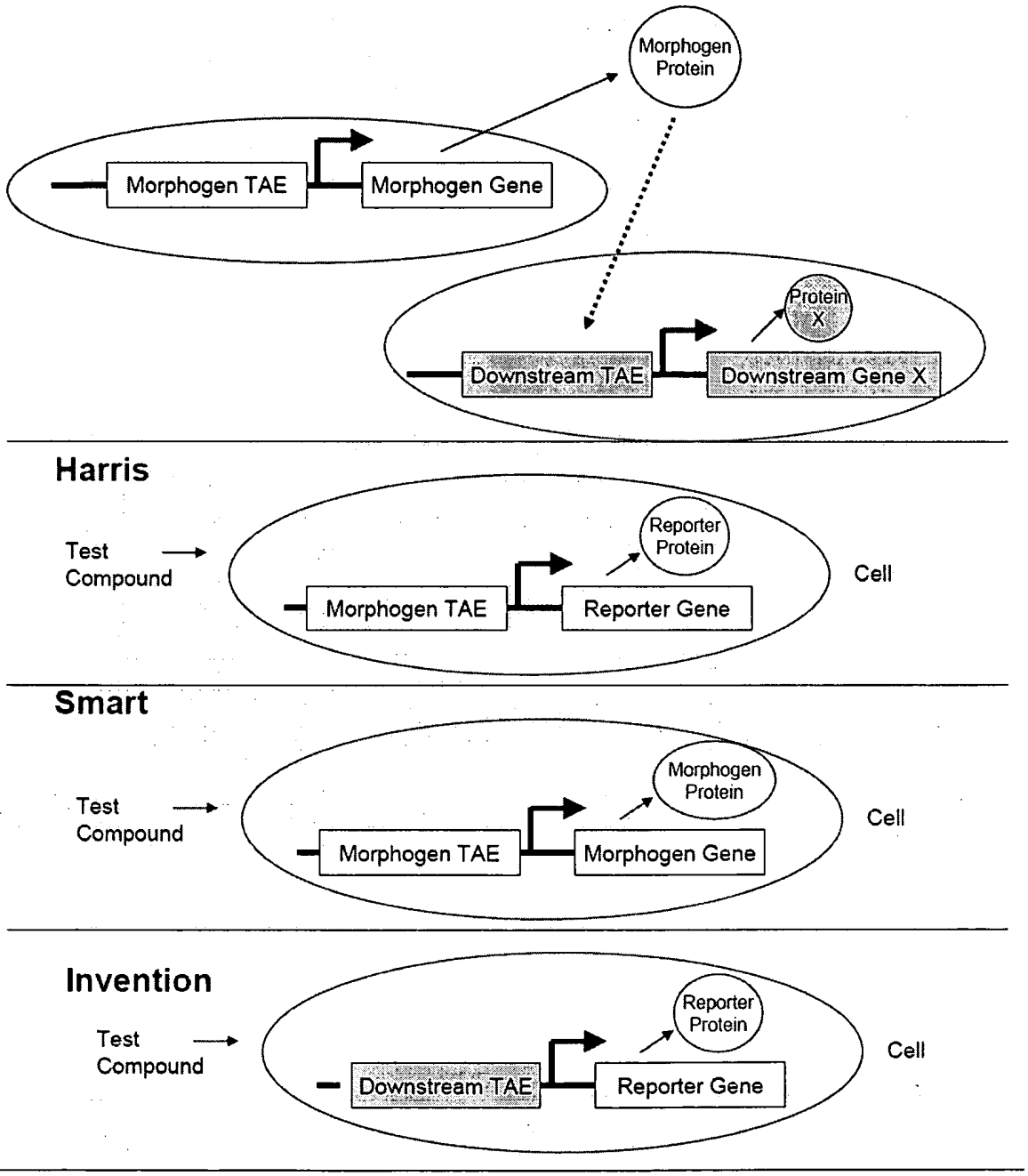
APPENDIX A


Morphogen Protein
Morphogen TAE
Morphogen Gene
Protein X
Downstream TAE
Downstream Gene X
Harris
Test Compound
Reporter Protein
Morphogen TAE
Reporter Gene
Cell
Smart
Test Compound
Morphogen Protein
Morphogen TAE
Morphogen Gene
Cell
Invention
Test Compound
Reporter Protein
Downstream TAE
Reporter Gene
Cell

APPENDIX B

Claims Involved in the Appeal of Application Serial No. 09/613177:

1. A method for identifying a compound that induces a morphogen-mediated biological effect, the morphogen selected from OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vgl, Vgr-1, DPP, or 60A, the method comprising:

(a) providing a test cell comprising a DNA comprising:

(i) a transcription activating element that is responsive to, and distinct from the gene encoding, said morphogen, and

(ii) a reporter gene encoding a detectable gene product, the transcription activation element being in operative association with the reporter gene,

wherein the reporter gene is transcribed when the DNA is present in a cell that is

(1) responsive to the morphogen, and

(2) contacted with said morphogen;

(b) exposing said test cell to a candidate compound; and

(c) detecting expression of said detectable gene product, wherein an increase in expression of said detectable gene product after exposing said test cell to said candidate compound indicates the ability of the compound to induce the morphogen-mediated biological effect;

wherein said morphogen-mediated biological effect requires the presence of said transcription activating element, so as to thereby identify a compound that induces a biological effect mediated by a morphogen.

2. The method of claim 1 wherein said transcription activating element binds with a protein having general DNA-binding properties of a MEF-2 family protein, said DNA binding being inducible by performing step (b).

3. The method of claim 1, wherein said transcription activating element comprises a sequence that hybridizes to an MEF-2 binding site sequence.

6. The method of claim 1 wherein said morphogen activating element comprises a sequence

of A and T residues.

9. The method of claim 6 wherein the A and T residues are adjacent to an AP-1 biding site sequence.

13. A method of producing a compound competent to induce a biological effect mediated by a morphogen selected from OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vgl, Vgr-1, DPP, or 60A, the method comprising:

a. obtaining said compound by screening at least one candidate compound according to the method of claim 1 or 2; and

b. producing said compound or a derivative thereof having substantially the same ability as said compound to induce said morphogen mediated biological effect.

36. A method for identifying a candidate compound that induces a biological effect mediated by a morphogen selected from OP-1, OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-9, Vgl, Vgr-1, DPP, or 60A, the method comprising:

(a) providing a test cell comprising DNA, said DNA comprising a transcription activating element that is responsive to, and distinct from the gene encoding, said morphogen, said DNA, when present in a cell responsive to said morphogen and contacted with said morphogen, serving to induce transcription of a gene operatively associated with said transcription activating element;

(b) exposing said test cell to a candidate compound; and

(c) detecting morphogen inducible DNA binding to said transcription activating element by a cellular protein, wherein an increase in said binding after exposing said test cell to said candidate compound indicates the ability of said candidate compound to induce said morphogen mediated biological effect,

wherein step (c) occurs within approximately 2-12 hours of completing step (b), and wherein said morphogen-mediated biological effect requires the presence of the transcription activating element.

43. The method of claim 1 wherein the morphogen is OP-1.

44. The method of claim 2, wherein said morphogen-responsive transcription activating element also binds with a second protein having general DNA-binding properties of an AP-1 family protein.

45. The method of claim 1, wherein the morphogen is OP-2, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, Vg1, Vgr-1, DPP, or 60A.

46. The method of claim 43 or 45, wherein the morphogen is of human origin.

47. The method of claim 1, wherein said morphogen-mediated biological effect is: stimulating proliferation of mammalian bone / cartilage progenitor cells, stimulating differentiation of mammalian bone / cartilage progenitor cells, supporting growth and maintenance of mammalian endochondrial bone tissue, delaying or mitigating the onset of senescence or quiescence-associated loss of phenotype or tissue function, stimulating phenotypic expression of differentiated cells, inducing redifferentiation of transformed cells, induction of VEGF expression, induction of PTH-mediated cAMP production in osteoblast, or induction of neuronal marker.

48. The method of claim 47, wherein said neuronal marker is L1 or N-CAM.

49. The method of claim 1, wherein said morphogen-mediated biological effect is induction of mitogenesis and phenotypic markers for chondrocyte or osteoblast differentiation.

50. The method of claim 49, wherein said phenotypic markers is: type I collagen, type II collagen, type X collagen, alkaline phosphatase, osteocalcin, N-cadherin, N-CAM, or MSX-2.